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10/651,582

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Anup Sood

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06/15/2006

GE HEALTHCARE BIO-SCIENCES CORP.
PATENT DEPARTMENT
800 CENTENNIAL AVENUE
PISCATAWAY, NJ 08855

EXAMINER

CALAMITA, HEATHER

ART UNIT

PAPER NUMBER

1637

DATE MAILED: 06/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|--|-----------------------------|--|
| Office Action Summary | Application No. 10/651,582 | Applicant(s) SOOD ET AL. | |
| | Examiner Heather G. Calamita, Ph.D. | Art Unit 1637 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 20 April 2006.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-40 is/are pending in the application.
- 4a) Of the above claim(s) 31-35 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-30 and 36-40 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 29 August 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date <u>06/28/04, 03/12/04</u> . | 6) <input type="checkbox"/> Other: _____ |

Art Unit: 1637

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of claims 1-30 and 36-40 in the reply filed on April 20, 2006 is acknowledged.

Status of Application, Amendments, and/or Claims

2. Claims 1-40 are currently pending. Claims 1-30 and 36-40 are under examination. Claims 31-35 are withdrawn as directed to non-elected subject matter.

Claim Rejections - 35 USC § 112 - Scope of Enablement

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for performing the method recited in claim 1 when the reacting step and the mixing step are carried out separately, does not reasonably provide enablement for performing the method recited in claim 1 when the reacting step and the mixing step are carried out simultaneously. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

Claim 1 is broadly drawn to detecting an analyte by conducting a nucleic acid polymerase reaction to produce a labeled polyphosphate and simultaneously reacting the labeled polyphosphate with a phosphatase to cleave the labeled phosphate and detect it. The invention is in a class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claim encompasses detecting an analyte by conducting a nucleic acid polymerase reaction to produce a labeled polyphosphate and simultaneously reacting the labeled polyphosphate with a phosphatase to cleave the labeled phosphate and detect it.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is no reasonable expectation of success. According to claim 1, the labeled polyphosphate is produced from at least one terminal phosphate-labeled nucleotide in the reacting step and the at least one terminal phosphate-labeled nucleotide can be a dNTP with a label on the terminal phosphate. Since it is known that phosphatase removes 5' phosphate groups from DNA and RNA, if the at least one terminal phosphate-labeled nucleotide is a dNTP with a label on the terminal phosphate, when the reacting step and the mixing step are carried out simultaneously, the dNTP with a label on the terminal phosphate is cleaved to an individual phosphate in the presence of phosphatase in step (a) of claim 1 and the method recited in claim 1 cannot be performed.

The unpredictability of the art and the state of the prior art

The art teaches that phosphatase cleavage of labeled terminal phosphate groups for analysis is not

Art Unit: 1637

unpredictable if the parameters are not flawed. As discussed supra Applicants methods are flawed. Since it is known that phosphatase removes 5' phosphate groups from DNA and RNA, if the at least one terminal phosphate-labeled nucleotide is a dNTP with a label on the terminal phosphate, when the reacting step and the mixing step are carried out simultaneously, the dNTP with a label on the terminal phosphate is cleaved to an individual phosphate in the presence of phosphatase in step (a) of claim 1 and the method recited in claim 1 cannot be performed.

Working Examples

The specification presents no working examples with respect to performing simultaneous reacting and mixing.

Guidance in the Specification.

The specification provides guidance for performing the method recited in claim 1 when the reacting step and the mixing step are carried out separately.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims and the lack of guidance provided in the specification, the unpredictability of the art, the presence of working examples relevant only to the method as recited in claim 1, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Art Unit: 1637

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 9, 10, 11 and 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Rothschild et al. (USPN 5,986,076).

With regard to claim 1, Rothschild et al. teach a method of detecting an analyte comprising the steps of:

a) anchoring said analyte to a nucleic acid template (see col. 36 lines 35-61, where the biotin is anchored to the primer nucleic acid);

(b) conducting a nucleic acid polymerase reaction to produce labeled polyphosphate, said reaction comprising the reaction of said template, a primer, at least one terminal phosphate-labeled nucleotide, and a nucleic acid polymerase (see col. 36 lines 35-61, where the PCR contains a biotin molecule on the 5' end of each complementary strand)

(c) analyzing said labeled polyphosphate (see col. 37 lines 20-25 and table, where the product is analyzed for disease).

With regard to claim 2, Rothschild et al. teach the primer is a nuclease resistant primer (see col. 36 lines 35-42, where the primer has biotin on the 5' end).

With regard to claim 3, Rothschild et al. teach the nucleic acid polymerase reaction further includes an enzyme having 3' --> 5' exonuclease activity (see col. 34 lines 11-12, where Taq polymerase is recited. Taq polymerase has 3'-5' exonuclease activity).

With regard to claim 5, Rothschild teaches further including the step of separating nucleic acid template not anchored before said conducting step (see col. 36 lines 35-61, where the primer template

Art Unit: 1637

complex is thermally separated from uncomplexed template nucleic acids).

With regard to claim 9, Rothschild teaches the analyte is DNA (see col. 36 lines 35-61).

With regard to claim 10, Rothschild teaches the analyte is anchored to said nucleic acid template by non-covalent binding, or by one or more covalent bonds (see col. 36 lines 35-61, where the biotin is anchored to the primer nucleic acid via a covalent bond).

With regard to claim 11, Rothschild teaches the nucleic acid polymerase is a DNA polymerase (see col. 34 lines 11-12, where Taq polymerase is recited. Taq polymerase is a DNA polymerase).

With regard to claim 13, Rothschild teaches the nucleic acid template and said primer are switched and it is said primer that is anchored to the analyte (see col. 36 lines 35-61, where the biotin is anchored to the primer nucleic acid and the primer hybridizes to the template).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims, 5, 7, 8, 15-30 and 36, 37, 38 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rothschild et al. (USPN 5,986,076) in view of Williams (USPN 6,255,083).

The teachings of Rothschild are described previously.

Rothschild does not teach the limitations of claims 4-8, 15-30 and 36-40.

With regard to claim 7, Williams teaches further comprising the step of characterizing said analyte (see col. 1-3, where genotyping or sequencing the target nucleic is characterizing the analyte).

Art Unit: 1637

With regard to claims 8 and 16, Williams teaches the detectable species is produced in amounts substantially proportional to the amount of analyte (see col. 1-3, where the amount of PPi released for sequencing is proportional to the starting amount of template to be sequenced).

With regard to claims 17 and 39, Williams teaches at least one terminal phosphate-labeled nucleotide includes four or more phosphate groups in the polyphosphate chain (see col. 5).

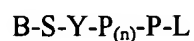
With regard to claim 18, Williams teaches the labels in at least one terminal phosphate-labeled nucleotide are enzyme-activatable labels selected from the group consisting of chemiluminescent compounds, fluorogenic dyes, chromogenic dyes, mass tags, electrochemical tags and combinations thereof (see col. 5).

With regard to claims 19 and 20, Williams teaches the terminal phosphate-labeled nucleotides carry distinct labels (see col. 1-3, where Williams teaches three types of dNTPs labeled on the gamma phosphate with different fluorescent labels).

With regard to claim 21, Williams teaches one or more additional detection reagents are added in said polymerase reaction of said conducting step, and said additional detection reagents are capable of a response that is detectably different from said labeled polyphosphate (see col. 1-3, where Williams teaches one or more additional detection reagents i.e. other three types of dNTPs labeled on the gamma phosphate with different fluorescent labels are added in the reaction in the reacting step).

With regard to claim 22, Williams teaches at least one terminal phosphate-labeled nucleotides are deoxy nucleotides and carry different labels (see col. 1-3).

With regard to claim 23, Williams teaches wherein at least one terminal-phosphate-labeled nucleotide is represented by the formula:



wherein P is phosphate (PO_3) and derivatives thereof, n is 2; Y is an oxygen or sulfur atom; B is a nitrogen-containing heterocyclic base; S is an acyclic moiety, carbocyclic moiety or sugar moiety; L is an

Art Unit: 1637

enzyme-activatable label containing a hydroxyl group, a sulfhydryl group or an amino group suitable for forming a phosphate ester, a thioester or a phosphoramidate linkage at the terminal phosphate of a natural or modified nucleotide, and P-L is a phosphorylated label which preferably becomes independently detectable when the phosphate is removed (see Figure 2).

With regard to claim 24, Williams teaches wherein said sugar moiety is selected from the group consisting of 2'-deoxyribosyl (see Figure 2).

With regard to claim 25, Williams teaches wherein said base is selected from the group consisting of uracil, thymine, cytosine, guanine, (see Figure 2).

With regard to claim 26, Williams teaches wherein said enzyme-activatable label is a fluorogenic dye (see Figure 2 and col. 5 lines 30-31).

With regard to claims 36 and 37, Williams teaches detection of a single base differences (see col. 1-3, where Williams teach genotyping of the analyte. Genotyping constitutes the detection of single base differences in the template).

With regard to claim 38, Williams teaches detecting the labeled polyphosphate (see the abstract, where Williams detects the release fluorescently labeled PPi).

It would have been prima facie obvious to use the method of anchoring the analyte to the template as taught by Rothschild with the detection method as taught by Williams in order to have a method where sequence information is produced continuously since Williams teach this is advantageous because the polymerases continually incorporate all four nucleotides into the nucleic acid chains and there is no loss of synchronization because single molecules are observed separately (see col. 1 lines 52-55). One of skill in the art would be motivated to use the use the method of anchoring the analyte to the template as taught by Rothschild with the detection method as taught by Williams so sequence information would be available without the need for a secondary assay to obtain genotype or sequence information.

Art Unit: 1637

6. Claims 4, 14, 15 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rothschild et al. (USPN 5,986,076) in view of Williams (USPN 6,936,702).

The teachings of Rothschild are described previously.

Rothschild does not teach analyzing using a labeled polyphosphate and a phosphatase to produce a detectable species characteristic of the analyte and detecting the cleaved labeled phosphate.

With regard to claims 4 and 40, Williams teaches the analyzing step includes (a) reacting said labeled polyphosphate with a phosphatase to produce a detectable species characteristic of said analyte and (b) detecting said detectable species (see col. 2-4).

With regard to claim 14, Williams teaches the primer and the template form a hairpin (see col. 6 lines 57-58).

With regard to claim 15, Williams teaches wherein said detectable species is detectable by fluorescence emission, (see col. 2-4).

It would have been prima facie obvious to use the phosphatase to cleave the labeled terminal phosphate for detection as taught by Williams in order to produce a detectable species (i.e. fluorescent PPi) from the labeled polyphosphate with the method of detecting an analyte as taught by Rothschild in order to produce a detectable species from the labeled polyphosphate since Williams teach that using a phosphatase will dephosphorylate fluorescent PPi and produce a detectable species (see col. 2-4). One of skill in the art would be motivated to use the use the phosphatase to cleave the labeled terminal phosphate for detection as taught by Williams in order to produce a detectable species (i.e. fluorescent PPi) from the labeled polyphosphate with the method of detecting an analyte as taught by Rothschild in order to produce a detectable species from the labeled polyphosphate.

7. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Rothschild et al. (USPN 5,986,076) in view of Williams (USPN 6,255,083).

Art Unit: 1637

The teachings of Rothschild are described previously.

Rothschild does not teach the nuclease resistant primer has a phosphorothioate linkage.

Nikiforov et al. teach a nuclease resistant primer with a phosphorothioate linkage (see col. 13, where Nikiforov discloses phosphorothioate nucleotides on a primer are for resisting exonuclease attack).

It would have been prima facie obvious to use the phosphorothioate linkage as taught by Nikiforov et al. with the method of detecting an analyte as taught by Rothschild in order to avoid nuclease degradation, since Nikiforov et al. using a phosphorothioate linkage prevents nuclease degradation of primers (see col. 13). One of skill in the art would be motivated to use the phosphorothioate linkage as taught by Nikiforov et al. with the method of detecting an analyte as taught by Rothschild to avoid nuclease degradation of the primers used in the method of detection.

8. Claims 28-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rothschild et al. (USPN 5,986,076) and Williams (USPN 6,255,083) in view of Mandecki (USPN 6,001,571).

The teachings of Rothschild and Williams are described previously.

Rothschild and Williams do not teach the enzyme activatable label is 5-bromo-4-chloro-3-indolyl phosphate as recited in claim 28 or the label is an alkaline phosphatase activated 1,2-dioxetane compound or a derivative thereof as recited in claims 29 and 30.

With regard to claim 28, Mandecki teaches the phosphorylated label is a chromogenic moiety is 5-bromo-4-chloro-3-indolyl phosphate or an alkaline phosphatase activated 1,2-dioxetane compound or a derivative of 1,2-dioxetane (i.e. adamantly 1,2-dioxetane) (see col. 3 lines 63-67 and col. 4 lines 1-12, where Mandecki teaches a label for oligonucleotides is a chromogenic moiety as recited in claims 28-30).

It would have been prima facie obvious to use 5-bromo-4-chloro-3-indolyl phosphate or an alkaline phosphatase activated 1,2-dioxetane compound or a derivative of 1,2-dioxetane (i.e. adamantly 1,2-dioxetane) as taught by Mandecki with the method of detecting an analyte as taught by Rothschild

Art Unit: 1637

and Williams as this is a simple substitution of equivalents. One of skill in the art would be motivated to use 5-bromo-4-chloro-3-indolyl phosphate or an alkaline phosphatase activated 1,2-dioxetane compound or a derivative of 1,2-dioxetane (i.e. adamantly 1,2-dioxetane) as taught by Mandecki with the method of detecting an analyte as taught by Rothschild and Williams since the label taught by Williams and the label taught by Mandecki are exchangeable.

Furthermore, the motivation to make the substitution cited above arises from the expectation the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose.

9. Claims 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rothschild et al. (USPN 5,986,076) and Williams (USPN 6,255,083) in view of Parker et al. (USPN 5,565,323).

The teachings of Rothschild and Williams are described previously.

Rothschild and Williams do not teach the enzyme activatable label is 5-bromo-4-chloro-3-indolyl phosphate as recited in claim 28 or the enzyme activatable label is a phosphorylated label and the fluorogenic moiety umbelliferyl phosphate as recited in claim 27.

With regard to claim 27, Parker et al. teach a chromogenic moiety of 5-bromo-4-chloro-3-indolyl phosphate or 4-methyl umbelliferyl phosphate (see col. 8 lines 56-67 and col. 9 lines 1-9, where Parker et al. teaches a label for an oligonucleotide is a chromogenic moiety as recited in claims 27 and 28).

It would have been prima facie obvious to use 5-bromo-4-chloro-3-indolyl phosphate or 4-methyl umbelliferyl phosphate as taught by Parker et al. with the method of detecting an analyte as taught by Rothschild and Williams as this is a simple substitution of equivalents. One of skill in the art would be motivated to use 5-bromo-4-chloro-3-indolyl phosphate or 4-methyl umbelliferyl phosphate as taught by Parker et al. with the method of detecting an analyte as taught by Rothschild and Williams since the label taught by Williams and the label taught by Parker et al. are exchangeable.

Art Unit: 1637

Furthermore, the motivation to make the substitution cited above arises from the expectation the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose.

Summary

10. No claims were allowed.

Correspondence

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 5:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at 571.272.0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number 571.273.8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to 571.272.0547.

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JEFFREY FREDMAN
PRIMARY EXAMINER
